REMARKS

In this non-final Official Action, the Examiners have provisionally rejected pending claims 11-15 under the judicially created doctrine of "obvious-type" double patenting. In addition, the Examiners have rejected pending claims 11-15 respectively under 35 U.S.C. 112, second paragraph, as being indefinite in language. Finally, the Examiners have rejected the pending claims under 35 U.S.C. 102(b) as being anticipated by the Blecha *et al.*PCT Publication, WO 96/32129.

In response, applicants have amended pending claims 11-15 respectively; and enclose herewith a Terminal Disclaimer signed by the attorney of record. By the present claim amendments, the documentary enclosure and the discussion presented hereinafter, applicants believe they have overcome and obviated each basis for rejection stated by the Examiners in the instant non-final Official Action.

Applicants and their undersigned attorney wish to state their intentions clearly. It is applicants express desire and purpose to advance the prosecution of this application on the merits, and not to delay or hinder its progress. It is a matter of formal record that this invention and patent application was filed on March 26, 1999; and the prosecution file history to date, now over five years in duration, is amply littered with a

broad range of questionable distractions, diversions, and digressions of varying kinds.

Nevertheless, it appears at last that the major issues are being addressed. It is the applicants' undersigned attorney's earnest hope that the Examiners presently of record will keep an open mind and have an unprejudiced approach concerning the substance of the core controversy now remaining in dispute; and also that the Examiners now of record will be able to recognize and appreciate the merits of a presented position which is opposite and stands in contradiction to the Examiner's stated point of view. On this premise, applicants will now address and review each of the different substantive bases for rejection stated by the Examiners in the instant Official Action with regard both to its legal requirements and the relevant factual circumstances.

I. The Obvious-Type Double Patenting Rejection

The Examiners have provisionally rejected claims 11-15 under the judicially created doctrine of "obvious-type" double patenting over claims 11-14 of co-pending U.S. Application Serial No. 10/391,155 (US2004/0009463). However, as the Examiners' have themselves noted (at page 2, middle of the instant Official Action), a timely filed Terminal Disclaimer in compliance with 37 C.F.R. 1.321(c) is legally sufficient and may be used to overcome a provisional rejection based on this non-statutory double patenting ground.

Applicants have chosen to respond to this ground of rejection by the filing of such a Terminal Disclaimer. Enclosed please find a properly prepared Terminal Disclaimer document, and the requisite fee payment of $55.00 as per 37 C.F.R. 1.20(d), which sets forth all the needed requirements and binding commitments of 37 C.F.R. 1.321; and is signed by applicants' attorney of record in accordance with 37 C.F.R. 3.73(b).

Accordingly, the filing of this Terminal Disclaimer and fee payment is a complete and appropriate response which overcomes the stated basis for rejection. For this reason, applicants request that the Examiners reconsider their stated position and withdraw this ground of rejection against the presently pending claims.

II. The Rejection Under 35 U.S.C. 112, 2nd Paragraph

The Examiners have rejected the original claims under 35 U.S.C. 112, 2nd paragraph as being vague and indefinite in language. The Examiners' position is based on the use of the terms "IκBα", "HIF-1α", and the phrase "without substantially altering" as these appear in different parts of the claims. In response, applicants direct the Examiners' attention to the multiple, substantive changes in the wording of independent claims 11 and 15 as presently amended.

In particular, the term "HIF-1α" has been replaced by the term

-- hypoxia-inducing factor (HIF)-1α --; and the term "IκBα" has been replaced by the term -- NFκB inhibitor IκBα --. Antecedent support for these word changes is found at Page 36, lines 18 and 19 respectively of the Specification text. These replacement terms are conventionally recognized and well understood within the scientific community as well as by persons ordinarily skilled in this art. As such, these replacement terms are deemed to be precise and definite nomenclature suitable for use in the claims.

As regards the Examiners' stated view that the phrase "without substantially altering" is unclear in its meaning, applicants' undersigned attorney respectfully submits that these are well recognized words of the English language; are words used every day in common parlance by English speaking people; and are words having long recognized and well understood dictionary definitions. Moreover, the term "substantially" has been adjudicated repeatedly in case law decisions as being sufficiently definite in meaning as well as being legally acceptable for inclusion within claim language. Similarly, the words "without" and "altering" are precise words having well established and commonly understood connotative and denotative meanings. Accordingly, applicants respectfully submit that there is nothing vague or indefinite about the meaning of this phrase as such; and there is no true basis for refusing to recognize and accept its clear meaning of this phrase within the language of the claims.

Accordingly, as regards the language of the pending claims as a whole, the essential inquiry is to determine whether the language of the pending claims do, in fact, set out and circumscribe a particular area or subject matter with a reasonable degree of precision and particularity. It is here where the meaning of the words and language employed to define the invention is analyzed; not in a vacuum, but always with regard to the teachings of the prior art and within the particular description, use or context disclosed by the Specification as it is understood and interpreted by one possessing ordinary skill in the pertinent art [In re Angstadt, 190 USPQ 214 (CCPA 1976)].

Finally, applicants note that each of the terms used in pending claims respectively is well understood; is not subject to numerous definitions and interpretations; and that there is no discrepancy, no confusion, and no ambiguity with regard to the antecedent descriptive basis and support provided by the Specification text. Rather, the language of the presently pending claims as a whole read on subject matter which is completely disclosed and enabled by the Specification text. Moreover, each recited element of the pending claims is explicit and clearly stated; and employs wording which sets forth and circumscribes the particular subject matter area with the requisite reasonable degree of precision and particularity [In re Moore, 169 USPQ 236 (CCPA 1971)].

For these reasons, applicants respectfully submit that each and every claim now pending satisfies the requirements of precision, clarity, and particularity required by the second paragraph of 35 U.S.C. 112. Accordingly, applicants respectfully request that the Examiners reconsider their stated position and withdraw this ground of rejection against the presently pending claims.

III. The Rejection Under 35 U.S.C. 102(b)

The Examiners have rejected claims 11-15 under 35 U.S.C. 102(b) as anticipated by the Blecha *et al.* publication [PCT International Publication No. WO 96/32129]. Applicants note also that this PCT printed publication is identical to the text of and claims the priority of U.S. Patent No. 5,830,993 - a prior art U.S. patent, which is already formally of record and constitutes a substantive part of the prosecution file history for this application.

The Examiners' view, as stated at page 6, middle of the instant Office Action, is that "... Blecha *et al.* teach the same truncated PR-39 peptides (e.g., PR-14 and PR-19) as the oligopeptides cited in claims 12, 13 or 14 (e.g., peptides comprising SEQ ID NO: 3, 4 or 5), and PR-14 and PR-19, which have the same structural features as the claimed PR-39 oligopeptides, e.g., having less than 26 amino acid residues, having N-terminal Arg-Arg-Arg, and having identical amino acid sequence to the N-terminal region of

Native PR-39 peptide". On this basis, the Examiners then conclude by stating ..."Thus, the properties of the claimed PR-39 oligopeptides such as inhibiting proteasome-mediated degradation, being pharmacologically active, or interacting with the α7 subunit of proteasomes in the cytoplasm of the cell would be expected for the peptides of PR-14 and PR-19, even though the cited properties are not indicated in the reference"....

In response, applicants respectfully submit and maintain that the Examiners' stated view and position concerning the teachings and suggestions of the Blecha *et al.* publication is factually inaccurate and is instead an unfortunate distortion of the information actually presented; that the Examiners have picked and emphasized only carefully selected portions of the Blecha *et al.* publication while concurrently omitting, ignoring and evading from other pertinent points of information within the publication; that the Examiners are legally in error as regards the legal prerequisites concerning the inherency doctrine with respect to anticipation under 35 U.S.C. 102(b); and that the Examiners' reliance upon the inherency doctrine is based solely upon a speculative theory which does not have an adequate basis to support it. Applicants will now demonstrate and evidence each of these stated positions.

A. The Relevant Legal Standards And Requirements

1. An anticipatory reference must describe the claimed subject matter with sufficient clarity and detail to establish that the subject matter existed in the prior art, and that such existence would be recognized by persons of ordinary skill in the filed of the invention [In re Spada, 15 U.S.P.Q.2d 1655 at 1657 (Fed. Cir. 1990)]. Anticipation, however, specifically requires that each element and every particular limitation set forth in the claim language be found, either expressly or inherently described, in a single prior art reference [Verdegaal Bros. Inc. v. Union Oil Co., 2 U.S.P.Q.2d 1051 at 1053 (Fed. Cir. 1987); Richardson v. Suzuki Motor Co., 9 U.S.P.Q.2d 1913 at 1920 (Fed. Cir. 1989)].

2. If a single prior art reference does not expressly set forth an element or particular limitation of the claim, that reference still may anticipate if that element or limitation is "inherent" in its disclosure. However, in order factually to establish inherency, the extrinsic evidence provided by the prior art reference must make clear that the missing descriptive matter is necessarily present in the disclosure of the reference, and that the disclosed extrinsic evidence would be so recognized by persons of ordinary skill in the technical field [Continental Can Co. USA Inc. v. Monsanto Co., 20 U.S.P.Q.2d 1746 at 1749 (Fed. Cir. 1991)].

3. Anticipation can be found only if the prior art reference discloses, either expressly or under principles of inherency, every limitation and function recited by the claim in question [RCA Corp. v. Applied Digital Data Systems Inc., 221 USPQ 385 at 388 (Fed. Cir. 1984)]. The limitations which must be met by an anticipatory reference are those set forth in each statement of function by the claims in question [In re Mott, 194 USPQ 305 at 307 (CCPA 1977)].

4. In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support a determination that the allegedly inherent characteristic necessarily flows from the teachings of the prior art reference [In re King, 231 USPQ 136 (Fed. Cir. 1986); W.L. Gore & Associates v. Garlock Inc., 220 USPQ 303 (Fed. Cir. 1983)]. In every instance, therefore, if an element or particular limitation recited by a claim is said to be inherently disclosed by a prior art reference, that element or limitation must be necessarily present within the reference in such a degree that a person of ordinary skill would clearly recognize its presence [Crown Operations Intl. Ltd. v. Solutia Inc., 62 U.S.P.Q.2d 1917 at 1921 (Fed. Cir. 2002); In re Robertson, 49 U.S.P.Q.2d 1949 at 1950-51 (Fed. Cir. 1999)].

5. It is incumbent upon the Examiner to identify wherein each and every facet of the claimed invention is disclosed within the applied reference [Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick, 221 USPQ 481 (Fed. Cir. 1984)]. However, if the Examiner fails to provide such facts or evidence, he has failed to discharge his legal burden and there is an insufficient basis to support any view that the claimed characteristic necessarily flows from or intrinsically exists within the prior art reference. Under these failed circumstances, the Examiner's view that the claims in question are inherently anticipated is completely erroneous, factually unjustified, and legally unsupportable [In re Levy, 17 USPQ2d 1461 at 1464 (BPAI 1990)].

6. In addition, it is well settled in law that anticipation is not established - if in reading a claim with respect to something disclosed in a prior art reference - the Examiner finds it necessary to pick, choose and combine various portions of the disclosure not directly related to each other by the teachings of the reference [In re Arkley, 172 USPQ 524 at 526 (CCPA 1972)]. Thus, when the Examiner cannot show any teaching in the applied reference which meets the corresponding requisite limitations and functions recited by the claims under review, no rejection based on anticipation is

correct, supportable, or legally proper [In re Oelrich, 212 USPQ 323 at 326 (CCPA 1981)].

7. Equally important, the substantive disclosure of the prior art reference must be so informative as to be enabling and so must place one of ordinary skill in possession of the claimed invention [Akzo N.V. v. U.S. International Trade Commission, 1 USPQ2d 1241 at 1245 (Fed. Cir. 1986); In re Wilder, 166 USPQ 545, 548 (CCPA 1970)]. The quality and quantity of knowledge and understanding to be derived from the prior art publication must be sufficient to allow those skilled in the art or science to understand the nature and operation of the invention as claimed [Seymour v. Osborn, 78 US 516 at 555 (U.S. Sup. Ct. 1870)].

B. Applicants Invention As Presently Claimed

Applicants' invention is claimed specifically as a "PR-39 derived oligopeptide family". This term, "PR-39 derived oligopeptide family", is defined by amended independent claims 11 and 15 respectively as a combination of requisite elements and particular limitations; and comprises a family whose individual members cause a selective inhibition of protease-mediated degradation in-situ after introduction intracellularly to a viable cell. In addition, several preferred embodiments of the membership constituting the PR-39 derived oligopeptide family are defined by dependent claims 12,

13 and 14 respectively as precisely recited amino acid residue sequences of differing lengths.

In particular, it will be noted and appreciated that the wording of presently amended independent claims 11 and 15 are broader definitions which encompass the commonly shared characteristics and properties of the 15, 11, and 8 amino acid residue length structures; and delineate a circumscribed membership which although size-limited, is pharmacologically active and functionally specific; and is structurally related as a family of short-length oligopeptides which are structurally analogous to the amino acid residue sequence to be found at the N-terminal end of the native PR-39 molecule.

In addition, the commonly shared pharmacologically active and functionally specific properties of this PR-39 derived oligopeptide family are overtly stated and clearly set forth as the requisite elements and specific limitations recited by amended independent claims 11 and 15 respectively. Thus, amended independent claim 11 (or claim 15) requires that each PR-39 derived oligopeptide family member present not less than six separate and individual traits and attributes. These are:

(1) a peptide which is pharmacologically active, but is less than 26 (or 20) amino acid residues in length;

(2) a peptide which is pharmacologically active and whose N-terminal amino acid residue sequence begins with Arg-Arg-Arg;

(3) a peptide which is pharmacologically active and is an analog of the amino acid sequence of native PR-39 peptide;

(4) a peptide which is pharmacologically active and selectively alters the proteolytic degradation activity of proteasomes in-situ;

(5) a peptide which is pharmacologically active and interacts in-situ with at least the $\alpha 7$ subunit of such proteasomes as are present within the cytoplasm of the cell; and

(6) a peptide which is pharmacologically active and able selectively to alter the proteolytic degradation activity of said proteasomes having an interacting $\alpha 7$ subunit such that the proteolytic degradation mediated by said interacting proteasomes against at least one peptide selected from the group consisting of NFκB inhibitor IκBα and hypoxia-inducing factor (HIF)-1α becomes inhibited without substantially altering other proteolytic degradation mediated by said proteasomes.

It will be noted and understood by the Examiners that amended independent claims 11 and 15 respectively set forth a precise recitation of the requisite elements and limitations comprising the minimal component parts of applicants' inventive subject matter as a whole; and that the

entirety of the claim language as recited constitutes and specifies the requisite elements and particular limitations of applicants' claimed invention.

C. The Content Of The Blecha *et al.* PCT Publication

1. The Blecha *et al.* publication explicitly discloses an attempt to synthesize peptide compositions of varying size and amino acid residue formulation in order to identify those peptide variants which are anti-microbial in effect and can be used to inhibit microbial growth and microbial infections [Page 1, lines 7-30].

2. Blecha *et al.* synthesized a range of differently formulated peptide variant sequences, all of which were loosely based on partial amino acid sequence fractions existing within the complete 39 amino acid residue length of the native PR-39 peptide. The native, 39 residue length, complete PR-39 peptide is a conventionally known peptide which was previously isolated from wound fluid and was shown to be biologically active for the induction of syndecan expression in mesenchymal cells [Page 1, lines 34-35; Page 2, lines 1-14].

3. The Blecha *et al.* fractionated peptides are shorter-length compounds in comparison to the known 39 residue structure of native PR-39

peptide; but are differently formulated experimental shorter length variants which were individually tested and empirically evaluated by Blecha *et al.* - in order to reveal which, if any, of these shorter length fractional sequences would retain and experimentally demonstrate the well-established anti-microbial properties of the native PR-39 peptide. The experimental protocol and empirical testing procedures conducted by Blecha *et al.* were directed solely and exclusively to reveal anti-microbial similar to those of native PR-39; and to demonstrate empirically whether or not the shorter length peptide fractions of differing formulations had any capacity for the active killing of microorganisms and/or the active suppression of microbial multiplication and/or growth [Page 3, lines 9-20].

4. The Blecha *et al.* publication sets forth the experimental test model; and discloses the use of a series of in-vitro assays to determine empirically which - if any - of the peptide fractional variants might possess and demonstrate the anti-microbial activity of the native PR-39 peptide structure. The empirical assays employed for revealing and demonstrating solely anti-microbial properties included: the gel-overlay assay, the lawn-spotting assay, the minimal inhibitory concentration test, the measurement of post antibiotic effects, the susceptibility of neutrophil phagocytosis, the regulation of neutrophil superoxide anion production, neutrophil chemotaxis capability,

and the influence on intestinal epithelial cells [Page 6, lines 16-34; Page 7, lines 1-34; Page 8, lines 1-21].

5. The Blecha *et al.* Publication then states that six variant shorter length fractionated peptide structures loosely based on the original PR-39 peptide were experimentally synthesized and empirically tested. The amino acid residue formulation of each variant peptide fraction which was experimentally evaluated is shown by Fig. 1 [Page 5, lines 31-35; Page 6, lines 1-15].

6. Each of these six variant Blecha *et al.* peptide fractions empirically evaluated had a different residue length and each had a different and individual amino acid residue formulation. Of these six, three synthesized variants were: PR-15, a fifteen residue length peptide structure constituting a fraction of the amino acid residues found at the COOH-terminal end of the native PR-39 peptide molecule; PR-16, a peptide sequence containing only the sixteen amino acid residue to be found at position nos. 11-26 in the native PR-39 peptide structure; and PR-23, a peptide sequence of twenty three residue length and having only amino acid residues to be found at position nos. 4-26 in the native PR-39 peptide. Thus, as a visual inspection of SEQ ID NOS: 6, 5 and 3 respectively in the publication shows, none of the

PR-15, PR-16 or PR-23 peptide structures contained an N-terminus sequence beginning with the amino acid resides Arg-Arg-Arg.

7. Consequently, of the six experimental peptide fractions empirically evaluated, only three variant peptides had an amino acid residue sequence which began with the amino acid residues found at the N-terminal end of the native PR-39 molecule, but were formulated as far shorter peptide structures. The three shorter-length structures are the PR-14 peptide fraction (a 14 amino acid residue length), the PR-19 peptide fraction (a 19 amino acid residue length), and the PR-26 peptide fraction (a 26 amino acid residue length) of native PR-39.

8. The Blecha *et al.* publication clearly and unequivocally presents the empirical results as to whether or not any of the six peptide variants retained and demonstrated the anti-microbial biological activity of the native PR-39 peptide. Blecha *et al.* expressly and overtly state the following:

(i) While PR-26 showed antibacterial activity against *E.* coli in the gel-overlay assay, the PR-14, PR-15, PR-16, PR-19, and PR-23 variants did not show such antibacterial activity [page 12, 19-22];

(ii) While PR-26 showed antibacterial activity in the lawn-spotting assay, the PR-14, PR-15, PR-16, PR-19, and PR-23 variants did not show such antibacterial activity [page 12, lines 23-29]; and

(iii) While PR-26 significantly reduced O_2 generation by intact neutrophils, the PR-14, PR-15, PR-16, PR-19, and PR-23 variants did not [page 15, lines 15-33].

9. In particular, among the three variant peptides whose formulations began with the amino acid residues found at the N-terminal end of the native PR-39 molecule, the PR-14 and the PR-19 variant peptides in particular failed to retain and failed to show any anti-microbial activity whatsoever [Page 15, lines 27-29]. Equally important, Blecha *et al.* observed and reported that, among the six variant peptides synthesized and experimentally tested, only the PR-26 peptide structure demonstrated any anti-microbial activity similar to that of the native PR-39 peptide [Page 12, lines 18-35; Page 13, lines 1-47].

10. The disclosure of the publication also explicitly states in detail what Blecha *et al.* believed are the direct teachings and overtly drawn conclusions for their own experimental tests and empirical results. These

are explicitly stated at page 12, lines 30-35 and page 13, lines 1-4 of the publication, and are summarized as follows:

(a) The COOH-terminus of the PR-39 structure does not contribute to antibacterial activity;

(b) The N-terminus of the PR-39 structure is not sufficient for antibacterial activity;

(c) The PR-26 peptide containing residue Nos. 1-26 of the original PR-39 structure is the antibacterial domain; and

(d) A particular secondary peptide structure conformation is required to exist and be present, as shown by both the PR-26 peptide and the original PR-39 original peptide, in order that the desired antibacterial activity exist.

11. The Blecha *et al.* publication also explicitly and repeatedly states that only one variant peptide structure, the PR-26 peptide variant, is demonstrably biologically active and is thus functional for the specific goal and stated purpose of anti-microbial activity. Of all six variant peptides synthesized and experimentally tested, only the PR-26 peptide variant is said to be suitable and useful via its demonstrated antibacterial properties [Page 13, lines 5-25]. The remaining five variant peptide structures, having no

effective or meaningful biological activity, are deemed to be of no technical consequence nor to have any scientific value whatsoever.

D. The Failure Of The Blecha *et al.* Publication To Teach Or Suggest The Requisite Limitations And Functions Of Applicants' Invention

As shown above, the Blecha *et al.* publication discloses only a very few facts, and these are of little relevance or import with respect to the expressly stated limitations and functions recited by the claims of applicant's invention. Applicants therefore direct the Examiners' attention to the following points.

(α) The sole and exclusive criteria of experimental evaluation for the described Blecha *et al.* peptide fractional variants are as anti-microbial agents. No other activity, property, or biological characteristic is revealed or suggested as being of possible value to Blecha *et al.*

Among the three variant peptides whose formulations began with the amino acid residues found at the N-terminal end of the native PR-39 molecule, the PR-14 and the PR-19 variant peptides in particular failed to retain and failed to show any anti-microbial activity whatsoever. Only one synthesized peptide variant of 26 amino acid residue length was empirically found to be biochemically active for its intended purpose. All the other Blecha *et al.* synthesized fraction variants shorter than 26 amino acid

residues in length had no anti-microbial activity; and thus had neither demonstrable biological activity nor any other functional use as such.

Equally important, there is no mention or inference by Blecha *et al.* of any other biological activity or function being of interest or of any technical worth. In particular, there is no hint that a completely different activity or function, such as proteolytic degradation by proteasomes, is of any relevance. Moreover, no facts or nor evidence of any kind are presented within the Blecha *et al.* publication which offers or provides any factual basis whatsoever for inferring or imputing any pharmacological activity for the Blecha *et al.* synthesized PR-14 and PR-19 fractional variants.

• Thus, in opposition and in direct contradiction to the Examiners' stated view and position - because the empirical data of Blecha *et al.* show that the PR-14 peptide fractional variant (a 14 amino acid residue length) and the PR-19 peptide fractional variant (a 19 amino acid residue length) demonstrated no anti-microbial activity - these shorter length peptides cannot rationally be expected to have any biological properties or traits at all; are, at most, logically expected to be biochemically and pharmacologically quiescent; and are seen as non-reactive peptide fractions having no biological activity or functional value.

• In addition, the Examiners' stated view - being in factual opposition and in direct contradiction to the reported empirical data of Blecha *et al* - is thus a *non sequitur*, an unreasonable conclusion that does not logically flow from its underlying premises; and is an unreasonable and irrational stance and personal opinion which does not have any factual underpinnings to support it. Clearly, the Examiners have chosen to draw inferences about alleged intrinsic biological properties from empirical evidence that not only denies the factual substance of this position, but also unequivocally demonstrates the PR-14 and PR-19 factional variants are biologically neutral and inert.

• Moreover, rather than accepting the Blecha *et al*. empirical evidence as actually presented and self-evaluated by the investigators themselves within their own publication, the Examiners have attempted to ignore and evade from the Blecha *et al*. results and data as reported - from which an ordinarily skilled person in the technical field could draw no inferences whatsoever regarding pharmacological activity. Instead, via the instant Official Action, the Examiners have created an artificial fiction and a self-generated facade - which is based on the bizarre and unsupported theory that intrinsic properties must somehow exist for these peptide fractions, if only because the structure of the native, complete 39 residue, PR-39 peptide has demonstrable anti-microbial properties. In effect, the Examiners have

drawn an inference from the specific (the anti-microbial properties of the native PR-39 peptide) and then unfairly and illogically presumed to apply the drawn inference to the general (the structure of the PR-14 and PR-19 peptide fractions).

Unfortunately, via this self-created technique, the Examiners have picked, chosen and combined various portions of the Blecha *et al.* disclosure not directly related to each other by the teachings of the reference. As a consequence, the Examiners do not and can not show any factual teaching or suggestion from the applied reference which meets the corresponding requisite limitations and functions recited by the claims under review; and, as a matter of adjudicated case law, an anticipation rejection based on such false presumptions is logically incorrect, is factually insupportable, and is legally erroneous.

(β) The mechanism for anti-microbial biological activity is elucidated by Blecha *et al.* within their own publication; and is revealed as a structural requirement which must be present before any shorter-length peptide fraction can become biologically active for its intended purpose, anti-microbial activity. As expressly set forth by Blecha *et al.*, the presence of the requisite anti-microbial domain within its peptide structure is an essential and necessary part of the variant fraction's formulation; and any variant

peptide formulation of any size which does not provide the required anti-microbial domain within its structure cannot provide any biological activity and thus is not functional for the Blecha *et al.* stated goal - the killing of microbes and the inhibition of microbial growth and infections. For these reasons, each of the other five synthesized peptide variants, and the PR-14 and PR-19 variant peptide fractions in particular, are abject empirical failures because they have no biological function or demonstrable activity.

As emphatically stated therein, the laboratory experiments and resulting empirical data presented within the Blecha *et al.* publication reveal that only the PR-26 peptide variant alone had any functional biological activity; that only the PR-26 peptide variant empirically showed the required anti-microbial killing properties using the in-vitro assays; and that none of the other five synthesized fractional peptide structures had any demonstrable biological activity whatsoever.

The direct teaching of Blecha *et al.* is therefore that the presence of an antibacterial domain as a distinct structural moiety is necessary and required within the peptide structure in order for antibacterial activity to exist and be demonstrated by the peptide variant; and, as proven by Blecha *et al.*, only the PR-26 peptide variant provides the requisite antibacterial domain within its peptide structure in a form comparable to that existing within the native PR-39 peptide.

• Therefore, in contradistinction to and unlike the stated view and position of the Examiners, the only justifiable inference concerning intrinsic properties and traits which could be possibly drawn concerning any biological activity and demonstrable function for a shorter length fractional peptide variant (based upon the structure of the native PR-39 peptide) is the presence of a structurally distinct antibacterial domain within that peptide variant. The demonstrable anti-microbial properties appear and disappear in direct correlation with the presence or absence of a structurally distinct antibacterial domain; and it is this structural domain which alone accounts for and demonstrably provides the requisite anti-microbial biological activity. Unfortunately, the Examiners have refused to consider or take notice of these undisputed facts.

• The Blecha *et al.* synthesized PR-14 and PR-19 peptide fractions are undisputably devoid of the structurally distinct antibacterial domain. Clearly, by the expressed views and evaluations of Blecha *et al.* themselves within their own publication, the absence of the structural antibacterial domain is given as the primary cause and overt factual reason why the PR-14 and PR-19 peptide fractions were found to be biologically inert while the PR-26 peptide fraction showed demonstrable anti-microbial properties. Nevertheless, the Examiners have refused to acknowledge these facts; and tacitly even denied their presence within the Blecha *et al.* publication.

However, it is legally incumbent upon the Examiner to identify wherein each and every facet of applicants' claimed invention is disclosed within the applied reference. As a consequence, because the Examiners have failed to provide such facts or evidence, the Examiners have failed to discharge their legal burden; and there is an insufficient factual basis to support any view that the claimed characteristic necessarily flows from or intrinsically exists within the prior art reference. Under these failed circumstances, as a matter of adjudicated case law decisions, the Examiners' conclusions that the claims now pending are inherently anticipated is completely erroneous, factually unjustified, and legally unsupportable.

(γ) As set forth within the cited and applied reference, the five failed variant peptides synthesized by Blecha *et al.* are merely laboratory test models and analytical tools employed as workpieces in a prepared experimental program to identify what constitutes the anti-microbial domain and where the anti-microbial domain is structurally to be found in the native PR-39 peptide. Also, by the express statements of Blecha *et al.* themselves, no worth or value is afforded to any of the five failed peptide variants; they are merely of minimal scientific interest as experimental means by which to elucidate the mechanism of anti-microbial killing activity.

• Accordingly, for each of the five fractional peptide variants (and the PR-14 and PR-19 fractional variants in particular) which empirically failed to show any anti-microbial activity, the consequence of their demonstrated failure to show biological activity results in them sharing a common category status as follows:

(i) Each failed variant peptide sequence synthesized by Blecha *et al.* is and remains merely a scientific curiosity having no scientific or technical value other than bare existence;

(ii) Each failed variant peptide sequence synthesized by Blecha *et al.* is and remains merely a laboratory model composition and analytical tool suitable only as a test workpiece in future research experiments; and

(iii) Each failed variant peptide sequence synthesized by Blecha *et al.* is and remains a substance without any known utility owing to the absence of having any empirically demonstrable biological activity.

In sum, all of these are explicit, direct and unrelenting outcomes for the Blecha *et al.* peptide variants as a structural class of compositions generally. Accordingly, as a matter of adjudicated case law, because the applied prior art reference does not expressly set forth the particular limitations and functions of the presently pending claims; and because the the prior art as such can not and does not provide the missing descriptive matter, there is no legal basis or rationale for the Examiners' view that the

requisite pharmacological activity would be inherently recognized for these Blecha *et al.* fractional peptide variants by persons of ordinary skill in the technical field

(δ) The Examiners have wrongly and improperly imputed the pharmacological activity and function of applicants' presently claimed invention as being among those conventional characteristics and functional traits previously known for native PR-39 peptide. The Examiners' erroneous view and position is presented at page 6, bottom of the instant Office Action.

• It will be noted and appreciated that the Blecha *et al.* publication is completely silent regarding the pharmacological activity of interacting with the α7 subunit of proteasomes in the cytoplasm of the cell; and selectively inhibiting proteasome-mediated degradation of specific peptides such as hypoxia-inducing factor (HIF)-1α and NFκB inhibitor IκBα intracellularly, while not interfering with the usual degradation of other peptides by these same proteasomes. None of these unique pharmacological activities and specific functions provided by applicants' claimed invention are conventionally known; and none of these activities are either contemplated or could be inferred intrinsically from the prior art, particularly not the Blecha *et al.* publication.

• Nevertheless, the Examiners have found it plausible to extrapolate these specific pharmacological activities and specific functions from the information and data presented by the Blecha *et al.* publication. Moreover, the Examiners have shown no hesitancy or reluctance to impute the presence and demonstrability of these specific pharmacological activities and specific functions to the PR-14 and PR-19 fractional peptide variants synthesized by Blecha *et al.* However, no facts, rationale or explanation is provided by the Examiners as the underpinnings to support their view and stance; only the subjective inherent imputation of these properties by the Examiners is deemed necessary in order to graft properties and traits artificially to the same PR-14 and PR-19 variants which Blecha *et al.* expressly state as having no demonstrable biological activity at all.

• Applicants and their undersigned attorney do not accept and expressly reject the Examiners' attempt to impute inherently and to graft artificially any pharmacological characteristic or biological trait. In short, the Examiners have forgotten that the sole source of such knowledge and information is the Specification text of the present application. Accordingly, the only suggestion for imputing such properties and traits stems from hindsight knowledge which the Examiners impermissibly derived from applicants' disclosure. In this manner, therefore, the Examiners have committed major prejudicial legal error.

E. The Examiners' Multiple Errors Of Law

Applicants respectfully submit and maintain that the Examiners' rationale and position as stated in the instant Office Action is centered on an erroneous and distorted interpretation of the legal doctrine of inherency. For this reason, a summary review of the legal doctrine of "inherent anticipation" is presented here.

1. Where the docine of "inherency" is applied to subject matter wherein all the elements of the invention as claimed are not shown in a single prior art reference, the legal requirement and proper standard to be met for anticipation has been set forth by landmark case of Continental Can Co. v. Monsanto Co. [20 USPQ2d 1746 (Fed. Cir. 1991)] as the following :

> "...To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill....
>
> This modest flexibility in the rule that "anticipation" requires that every element of the claims appear in a single reference accommodates situations where the common knowledge of technologists is not recorded in the reference; that is, where technological facts are known to those in the field of the invention, albeit not known to judges...." [20 USPQ2d at 1269-1270].

2. The basis of "inherency" thus requires a factual determination of whether those aspects of the claimed subject matter that are not directly taught in the single prior art reference - the missing descriptive information - were nonetheless known in the field of the invention by practitioners ordinarily skilled in that technical area [EMI Group North America Inc. v. Cypress Semiconductor Corp., 60 USPQ2d 1423 (Fed. Cir. 2001)]. Inherency, as a legal tool, must therefore supply those aspects of the claimed invention which are missing and absent from the incomplete description in the single prior art reference; and must provide credible facts and evidence that the ordinarily skilled practitioner in the art is at least acquainted with, if not fully cognizant of, the missing descriptive aspects.

This legal foundation - that a person of ordinary skill in the relevant art must acknowledge or be aware that the missing descriptive aspects are present as part of a commonly-available body of knowledge and information in the technical field - is a crucial and essential point of law. Moreover, such factual acknowledgment or common awareness by persons of ordinary skill in the art is critical for establishing and credibly demonstrating that the missing descriptive subject matter would intrinsically be present for every embodiment defined by the requisite elements and limitations of the claim language [Finnigan Corp. v. ITC, 51 USPQ2d 1001 (Fed. Cir. 1999)].

3. Inherency, however, can not be established either by "probabilities" or "possibilities". The mere hypothesis that an outcome might result from a given set of circumstances is not sufficient [In re Oelrich, 212 USPQ 323 at 326 (CCPA 1981)]. Thus inherency, as a basis for rejection, is available only when the specific element or particular limitation defined in a claim can be identified and supplied by the ordinary skilled practitioner in the technological field from the disclosure of the single prior art reference with substantial certainty.

Accordingly, probabilities and speculation are not a substitute for substantial certainty and are not sufficient in fact or law to invoke or apply the inherency doctrine [In re Chandler, 117 USPQ 361 (CCPA 1985); In re Wertheim, 191 USPQ 90 (CCPA 1976)]. Moreover, in order for a claimed invention to be inherently disclosed, the invention defined and claimed by applicants must be the sole necessary and only reasonable construction to be given to the prior art disclosure; and the all the elements, particular limitations, and results recited by the wording of applicants' claims must inevitably exist and be revealed by the cited and applied prior art. [In re Robertson, 49 USPQ2d 1949 (Fed. Cir. 1999)].

4. It is also important to note that the legal burden to establish inherency as a basis for rejection lies exclusively upon the Examiners. The Examiners themselves must demonstrate that the prior art reference,

directly or indirectly, discloses and provides all the requisite elements and particular limitations defined by the claim, as well as identifies the resulting capabilities, properties, and traits recited by the claim language with substantial certainty.

If, however, the prior art reference, directly and indirectly, does not describe the claimed subject matter with sufficient clarity and detail to establish that the invention as a whole was known in the prior art and that such information would be at least acknowledged by persons of ordinary skill in the field of the invention, then the single reference is legally inadequate and factually insufficient as a basis for an inherent anticipation rejection [Crown Operations Intl. Ltd. v. Solutia Inc., 62 USPQ2d 1917 at 1921 (Fed. Cir. 2002)].

F. Applicants' Conclusions

It is applicants' view and position that the Examiners' use of the inherency doctrine and their reliance upon "anticipation" as a basis for rejection fails to meet the necessary minimal factual requirements because of the glaring factual deficiencies and the absence of essential descriptive subject matter within the Blecha *et al.* reference. Moreover, because the disclosure of the Blecha *et al.* reference is so blatantly deficient in essential descriptive information, applicants maintain that the rationale employed by the Examiners as the underlying basis for rejection is factually non-existent,

is purely speculative, and is without substantive evidentiary foundation or support as such.

Applicants submit that, under the present circumstances, the inherency doctrine for anticipation may not be properly employed as a legal basis for rejection of the claims. Applicants' position is amply demonstrated and fully supported by the absence of relevant supporting facts, pertinent information, useful knowledge, or data within the single cited and applied reference, the Blecha *et al.* publication.

Applicants' also note that, as a matter of law, the underlying basis of "inherency" requires a factual determination of whether those aspects of applicants' claimed subject matter that do not exist in and are not directly taught by the Blecha *et al.* reference - *i.e.,* the missing essential descriptive information - were nonetheless known in the field of the invention by practitioners ordinarily skilled in that technical area. Thus, to employ "inherency" as the legal basis for rejection, the Examiners must first supply those missing descriptive aspects of applicants' claimed invention which are absent from the incomplete disclosure of the Blecha *et al.* publication; and the Examiners must then also provide credible facts and probative evidence that the ordinarily skilled practitioner in the art is at least acquainted with, if not fully cognizant of, the missing descriptive aspects which pertain to and bear upon applicants' claimed subject matter as a whole.

The Examiners, however, have failed to provide any extrinsic information, data and knowledge at all - a legal burden which is their sole and exclusive obligation. Furthermore, such extrinsic knowledge must be presented by the Examiners in order to support their rejection basis because the cited and applied Blecha *et al.* reference is so utterly lacking in information and is clearly deficient in presenting the requisite elements and particular limitations recited by applicants' claimed invention.

The extrinsic evidence which is legally required, and is yet to be provided by the Examiners, must provide the essential missing descriptive matter to serve as a foundation; and be sufficient in factual content that a person of ordinary skill in the relevant art would acknowledge or would be aware that the missing descriptive aspects which are absent and omitted from the Blecha *et al.* disclosure are indeed present as part of a commonly-available body of knowledge and information in the technical field. Moreover, such factual acknowledgment or common awareness by persons of ordinary skill in the art is critical for establishing and credibly demonstrating that the missing descriptive subject matter would intrinsically be present in every embodiment defined by the requisite elements and limitations of applicants' claim language.

For the reasons presented above, applicants thus find the Examiners' stated views and conclusions to be factually inaccurate and legally erroneous

with respect to applicants' claimed invention. The Examiners' stated reasons for using the inherency doctrine and for employing anticipation as a rejection basis have been shown to be unsupportable, unjustified and erroneous in their entirety. Accordingly, for all these reasons, applicants respectfully request that the Examiners reconsider their stated position and withdraw this ground of rejection against the presently pending claims.

Finally, applicants have addressed each basis of rejection stated in the instant Official Action forthrightly and objectively. In applicants' view, each relevant issue or controversy has been evaluated, acted upon and resolved completely. For these reasons, applicants respectfully submit and affirm that amended claims 11-15 now pending are therefore now allowable.

In view of the above discussion and detailed review, applicants believe that this case is now in condition for allowance and reconsideration is respectfully requested. The Examiners are invited to call applicants' undersigned attorney should they feel that such a telephone call would further the prosecution of the present application.

Respectfully submitted,

MICHAEL SIMONS
YOUHE GAO

Date: August 10, 2004 By: _____

David Prashker
Registration Number 29, 693
Attorney for applicants
P.O. Box 5387
Magnolia, Massachusetts 01930
Tel: (978) 525-3794